wherein said fused chemeric toxin product comprises a linear protein sequence.

REMARKS

Applicants would like to thank Examiner Helms for courtesy shown their representative during several recent telephone conferences. The above amendments to claim 1 and the addition of claim 29 serve to better define the starting materials used to make the instant claimed compounds as well as to provide a further characterizing feature of the instant claimed products. These features have been discussed with Examiner Helms during the referred to telephone conferences.

Specifically, claim 1 has been amended to recite that the claimed chemeric toxins are the genetic engineering fusion products of a cell targeting moiety and a cell killing moiety. The chemeric toxin product is specifically characterized as consisting essentially of a linear polypeptide. In other words, the starting materials in claim 1, A and B, are linked directly together to form a linear polypeptide and are not linked through intermediate linking moieties as is shown in the prior art. Further, the claimed product is characterized as binding to binding sites on cells that have not previously been known to have gonadotropin releasing hormone binding sites. The characterizing binding sites that have been set forth in amended claim 1 are different from the conventional human pituitary GnRh receptors that are known today and are referred to as "GnRH receptor type I".

Thus, there are at least two differentiating characteristics of the products claimed herein as compared to the products that have been disclosed in the prior art. First, there is the fact that the instant claimed products bind to previously unknown and unrecognized binding sites as well conventional binding sites. Second is the fact that the claimed chemeric toxin consists essentially of the reference components A and B, and is a linear protein sequence. Therefore the claimed product does not have linking moieties therein that

are attached through specific R groups of one of the amino acids. New claim 29 addresses one very specific difference between the products being claimed herein and the products that have been disclosed in the prior art. In the prior art (as exemplified by the Lombardo reference), the disclosed GnRH molecule starts with the moiety "Q", which can be PyroGlu-His-Trp; or N-acetyl-4-Phe^{1,2}-Trp; or 3-indolylproprionyl. Clearly, therefore, claim 29 is distinct from the state of the prior art as set forth in the references that have been cited by the examiner.

Examiner Helms has contended that the instant claimed products are at least obvious from a consideration of the state of the prior art. Specifically, Examiner Helms has alleged that substituting fusion of starting materials by genetic engineering techniques is an obvious variant of reacting the same two starting materials by more conventional chemical reaction means. That may or may not be true. However, two points overcome this obviousness based reasoning. First, the staring materials of the prior art are not the same as the starting materials of this instant invention. In the prior art, the starting materials, while perhaps based on a toxin and a cell targeting moiety encoding GnRH, also contain linking moieties that have been added to the base reactant compounds in order to enable these compounds to be joined through these linking moieties. So, while a portion of the prior art staring materials may have similar structure to a portion of the instant starting materials, they are not the same. If the starting materials of the prior art, including the attached linking moieties, were to be ligated through genetic engineering techniques, the resulting product would not be the same as that instant claimed product because the prior art product, whether made by conventional or genetic engineering techniques, would still have the linking moieties thereon, whereas the instant claimed product does not. It is unobvious to react different starting materials, than have been disclosed in the prior art, to make different products than those that have been disclosed in the prior art. A person of ordinary skill in this art, would not have any impetus to make the instant claimed products (without linking agents). A person of ordinary skill in this art would not have attempted to make the linear

polypeptides being claimed when it was known to make other compounds using similar, but markedly different, starting materials.

Second, it is clear that the instant claimed products are unobviously different from any that have been known in the prior art. Prior to this invention, it was not known that there were GnRH binding sites on adenocarcinoma cells. Since the advent of this invention, the existence of such new sites has been confirmed by other workers in the field. The several papers that were presented to the examiner in the original of this application amply support the fact that these new and previously uncloned sites exist and that they are different from known and cloned human pituitary GnRH receptors that are now known and are currently referred to as "GnRH receptor type I". Since these sites were not known prior to the instant invention, it would not have been obvious to a person of ordinary skill in this art to make a chemeric toxin to bind to these sites.

The previously known compounds in this technology were not known or disclosed to be useful in the treatment of adenocarcinomas. The compound products of this invention are effective against these diseases. This is an unobvious result that would not have been apparent to a person of ordinary skill in this art.

Obviousness is closely related to expectedness and predictability. If a claimed compound has a different utility than the closest compounds of the prior art, that is usual an indication that the newly claimed compound is unobvious from the state of the prior art. A patent is granted for a contribution to the general fund of human knowledge. The matter being contributed must enrich the fund of knowledge. In this case, it should be clear that producing a new compound that should have behaved in a manner that is similar to the closest prior art compound is unobvious when the new compound not only behaves like the prior art compounds, but has new and unusual additional properties and utilities.

The examiner's attention is directed to pages 3 and 11, amongst others, where the specific features of the instant claims are set forth. It is therefore believed that these proposed amendments are supported by the instant specification and present no prohibited new matter. It is believed that the entry of these amendments is therefore appropriate.

With the entry of these amendments, the instant claims are in condition for allowance because they recite features that are neither set forth in the references nor that would have been obvious to a person of ordinary skill in the art from a consideration of the disclosures of the references.

Respectfully submitted,

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COPY OF CLAIM SHOWING AMENDMENTS

1. (Four times amended) Targeted fused chimeric toxins comprising a genetically engineered molecule produced by fusing, [fused] at the level of cDNA: [, comprising]

A. at least one cell targeting moiety encoding GnRH [and] or GnRH analog that is adapted to recognize specific cells bearing gonadotropin releasing hormone binding sites; and

B. at least one cell killing moiety that is adapted to kill specific cells bearing gonadotropin releasing hormone binding sites,

wherein the at least one cell targeting moiety consists essentially of gonadotropin releasing hormone and the at least one cell killing moiety consists essentially of a cell killing toxin;

wherein said chimeric toxins are adapted to bond to GnRh binding sites on adenocarci[e]noma cells, benign uterine lyomyoma cells, endometrial island cells and/or pituitary tumor adenoma cells ; and

wherein said chemeric toxin is a linear protein consisting essentially of peptide bonds.

2. (Three times amended) Targeted fused chimeric toxins according to claim 1 wherein the specific cells bearing gonadotropin releasing hormone binding sites are malignant adenocarcinoma cells.